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10/573,691	02/22/2007	Fariba Nayeri	25401-45US	7139

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,691	NAYERI ET AL.	
	Examiner	Art Unit	
	UNSU JUNG	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *12 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 13-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/31/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of species 4 (stool, claim 2) from List I and species 1 (bowel disease/inflammatory bowel disease, claims 11 and 13) from List II in the reply filed on August 20, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-11 and 13-21 read on the elected species.

Status of Claims

2. Claims 1-22 are pending, claims 12 and 22 have been withdrawn from consideration, and claims 1-11 and 13-21 are currently under consideration for patentability under 37 CFR 1.104.

Priority

3. It is noted that this application appears to claim subject matter disclosed in prior Application No. PCT/IB04/03606, filed September 29, 2004 and 60/507,192, filed September 29, 2003. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e.,

continuation, divisional, or continuation-in-part) of all nonprovisional applications. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was

unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Signature date of Tayeb Nayeri is missing.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on July 31, 2006 has been considered by the examiner. However, non-patent literature references Mitsutka et al., Yoshihisa et al., and Jacek et al. has not been considered as copies of the three non-patent literature references have not been provided. Minor corrections were further made to include publication year 1994 for Miyazawa et al. and correct page number (500-504) for the first occurrence of Nayeri et al.

Specification

6. The use of the trademark BIOCORE™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112, First Paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. All non-patent literature prior art references cited in the written description and enablement rejections set forth below have been cited in the IDS dated July 31, 2006 with the exception of Vasan reference (*Circulation*, 2006, Vol. 113, pp2335-2362).

9. Written Description

Claims 1-11 and 13-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP stats that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." MPEP § 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. The MPEP states that:

"The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice…or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a

known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus" MPEP § 2163.

The MPEP does state that for a generic claim, the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitutes a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosures of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli* 872, F.2d at 1012, 10 USPQ2d at 1618.

The claims lack adequate written description for the following reasons. Independent claim 1 recites a method and device for diagnosing/evaluating an inflammatory disorder by determining relative levels of different forms of hepatocyte growth factor (HGF) in a body fluid sample from the individual and correlating the determined levels to an inflammatory disorder. The claims therefore broadly drawn to method and device for diagnosing an inflammatory disorder by assessing relative levels of different forms of HGF in the body fluid sample from the individual.

The specification discloses that HGF (also known as scatter factor, SF) is a unique growth factor, which is unrelated to other well-known polypeptide mitogens. HGF is secreted in response to cell damage and appears to be important for the regeneration

of certain organs and healing of wounds (Arakaki et al. *Hepatology*, 1995, Vol. 226, pp1728-1734). It is a heterodimer, having disulphide bonded heavy and light chains of approximately 60 and 30 kDa respectively, first synthesized as an inactive precursor (Miyazawa et al., *J. Biol. Chem*, 1994, Vol. 269, pp8966-8970). HGF is produced and is present in high concentrations at sites of organ damage (Nayeri et al., *Scand. J. Infect. Dis*., 2002, Vol. 34, pp500-504). The systemic and local production of HGF in various infectious diseases has been studied and high serum HGF concentrations have been observed during acute infectious diseases such as gastroenteritis, sepsis, pneumonia, skin and soft tissue infections and pyelonephritis (Nayeri et al., *Scand. J. Infect. Dis*., 2002, Vol. 34, pp500-504). Simultaneous with enhanced systemic production of HGF, high HGF concentrations have been found in cerebrospinal fluid during meningitis (Nayeri et al., *J. Infect. Dis*., 2000, Vol. 181, pp2092-2094). Raised HGF concentrations in exhaled breath condensate (Nayeri et al., *Respir. Med*., 2002, Vol. 96, pp115-119) in patients with pneumonia, which had no correlation to serum levels of HGF, indicated a local production of HGF during pneumonia. Some studies have found correlation between acute renal failure and increased urine concentrations of HGF (Taman et al., *Clinical Nephrology*, 1997, Vol. 48, pp241-245 and Goldberg et al., U.S. Patent No. 5,656,443). Further studies have found high levels of SF in urine and tumor tissues in patients with bladder cancer (Rosen et al. *J. Urol*, 1997, Vol. 157, pp72-78) and increased HGF in patients with pulmonary fibrosis (Yamanouchi et al. *Respir. Med*., 1998, Vol. 92, pp273-278).

Based on these teachings of the prior art, HGF has been implicated in a variety of disease conditions including inflammatory (pneumonia, acute renal failure, infectious diseases, etc.) and non-inflammatory (cancer and pulmonary fibrosis) conditions. The current state of the art (Vasan, *Circulation*, 2006, Vol. 113, pp2335-2362) of cardiovascular disease teaches that biomarkers are used to identify high-risk individuals to diagnose disease conditions promptly and accurately (p2335). Vasan further teaches that biomarkers can be used as indicators of disease trait (risk factor or risk marker) and diagnostic markers (recognizing overt disease, p2335, right column, first paragraph). For diagnostic markers, features such as high sensitivity, specificity, and predictive values are important (p2336, left column and Table 2). Consistent with teachings of Vasan, Matsumoto et al. (*Biochem. Biophys. Res. Comm.*, 1996, Vol. 221, pp391-395) teaches that the finding of increased HGF levels correlated with myocardial infarction is preliminary and further study is necessary to determine sensitivity and specificity in large number of patients (p395). HGF has been implicated in a variety of disease conditions including inflammatory (pneumonia, acute renal failure, infectious diseases, etc.) and non-inflammatory (cancer and pulmonary fibrosis) conditions as set forth above. Therefore, HGF does not satisfy features of diagnostic markers for inflammatory disorder as recited by the claims since HGF levels has been implicated with non-inflammatory disease conditions such as cancer and pulmonary fibrosis and does not meet the specificity requirement for a diagnostic marker.

The claims are directed to using any body fluid sample for detection of an inflammatory disorder. The sample can be selected from whole blood, serum, plasma,

stool, urine, cerebrospinal fluid, bronchoalveolar lavage, sputum, exhaled breath condensate, semen, saliva, joint fluid, or ulcer secrete and the inflammatory disorder can be selected from bowel disease, CNS disorder, lung disease or injury, kidney disorder, periodontal disorder, peritoneum, pericardium, pleura, or joint disorder. However, the specification only provides data for detecting HGF levels in feces/stool in patients with acute gastroenteritis and chronic inflammatory bowel diseases and HGF levels in skin biopsies in patients with chronic leg ulcer (Examples). Claims are further directed to using relative levels of different forms of HGF. However, the specification fails to provide any examples of how the relative levels of HGF are used to detect/diagnose an inflammatory disorder. Therefore, the specification fails to teach the skilled artisans how to detect all inflammatory disorders in all sample types and how to use this information in identifying the presence or absence of an inflammatory disorder amongst a plurality of inflammatory disorders.

Since the method and device for diagnosing/evaluating an inflammatory disorder by determining relative levels of different forms of HGF is not known in the prior art, the specification, in failing to disclose how the data assessing the relative levels of different forms of HGF is used to detect/diagnose an inflammatory disorder in an individual, the instant specification would not reasonably convey possession of the entire scope of the claimed invention to one of ordinary skill in the art.

Accordingly, it is deemed that the specification fails to provide adequate written description for the methods for method and device for diagnosing/evaluating an inflammatory disorder by determining relative levels of different forms of HGF and does

not reasonably convey to one of ordinary skill in the art that the inventor(s), at the time of the application was filed, had possession of the entire scope of the claimed invention.

10. Enablement

Claims 1-11 and 13-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention is drawn to methods and device for diagnosing/evaluating an inflammatory disorder by determining relative levels of different forms of HGF in a body fluid sample from the individual and correlating the determined levels to an inflammatory disorder. The claims therefore encompass methods and device for diagnosing/evaluating an inflammatory disorder by determining relative levels of different forms of HGF in a body fluid sample from the individual and correlating the determined levels to an inflammatory disorder.

The claims are directed to using any body fluid sample for detection of an inflammatory disorder. The current specification discloses that sample can be selected from whole blood, serum, plasma, stool, urine, cerebrospinal fluid, bronchoalveolar lavage, sputum, exhaled breath condensate, semen, saliva, joint fluid, or ulcer secrete and the inflammatory disorder can be selected from bowel disease, CNS disorder, lung disease or injury, kidney disorder, periodontal disorder, peritoneum, pericardium, pleura,

or joint disorder. However, the specification only provides data for detecting HGF levels in feces/stool in patients with acute gastroenteritis and chronic inflammatory bowel diseases and HGF levels in skin biopsies in patients with chronic leg ulcer (Examples). Claims are further directed to using relative levels of different forms of HGF. However, the specification fails to provide any examples of how the relative levels of HGF are used to detect/diagnose an inflammatory disorder. Therefore, the specification fails to teach the skilled artisans how to detect all inflammatory disorders in all sample types and how to use this information in identifying the presence or absence of an inflammatory disorder amongst a plurality of inflammatory disorders.

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Based on these teachings of the prior art, HGF has been implicated in a variety of disease conditions including inflammatory (pneumonia, acute renal failure, infectious diseases, etc.) and non-inflammatory (cancer and pulmonary fibrosis) conditions. The current state of the art (Vasan, *Circulation*, 2006, Vol. 113, pp2335-2362) of cardiovascular disease teaches that biomarkers are used to identify high-risk individuals to diagnose disease conditions promptly and accurately (p2335). Vasan further teaches that biomarkers can be used as indicators of disease trait (risk factor or risk marker) and diagnostic markers (recognizing overt disease, p2335, right column, first paragraph). For diagnostic markers, features such as high sensitivity, specificity, and predictive values are important (p2336, left column and Table 2). Consistent with teachings of Vasan, Matsumoto et al. (*Biochem. Biophys. Res. Comm.*, 1996, Vol. 221, pp391-395)

teaches that the finding of increased HGF levels correlated with myocardial infarction is preliminary and further study is necessary to determine sensitivity and specificty in large number of patients (p395). HGF has been implicated in a variety of disease conditions including inflammatory (pneumonia, acute renal failure, infectious diseases, etc.) and non-inflammatory (cancer and pulmonary fibrosis) conditions as set forth above. Therefore, HGF does not satisfy features of diagnostic markers for inflammatory disorder as recited by the claims since HGF levels has been implicated with non-inflammatory disease conditions such as cancer and pulmonary fibrosis and does not meet the specificity requirement for a diagnostic marker.

In summary, the specification fails to teach that the claimed methods and device can be used for diagnosing/evaluating an inflammatory disorder by determining relative levels of different forms of HGF in a body fluid sample from the individual and correlating the determined levels to an inflammatory disorder. In particular, the specification fails to teach one of ordinary skill in the art how to diagnose and/or detect an inflammatory disorder since the specification fail to disclose any method steps for how to detect one inflammatory disorder from a set of inflammatory disorders by determining relative levels of different forms of HGF in a body fluid sample from the individual. The specification fails to provide guidance for diagnosing/evaluating an inflammatory disorder by determining relative levels of different forms of HGF in a body fluid sample from the individual and correlating the determined levels to an inflammatory disorder. The prior art also fails to teach that relative levels of different forms of HGF can be used as a diagnostic marker for an inflammatory disorder. Consequently, the

specification fails to teach one of ordinary skill in the art how to make and use the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-11 and 13-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-11 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a step of diagnosing an inflammatory disorder based on relative levels of different forms of HGF. Claim 1 recites a method for diagnosing an inflammatory disorder in the preamble. Therefore, claims must recite a step of diagnosing an inflammatory disorder based on relative levels of different forms of HGF in order for the claims to be commensurate in scope with the intended purpose of the claimed method.

b. In claims 1-11 and 13-21, the term “different forms of HGF” is vague and indefinite. The specification does not define the term “different forms of HGF.”

Although the known forms of HGF include a precursor/single-stranded form and an active/double-stranded form as set forth below, the lack of specific definition of the term “different forms of HGF” may include forms other than the precursor and active forms and it is unclear what is encompassed by the term “different forms of HGF.”

c. In claims 10, 17, and 18, the term “bound analyte" is vague and indefinite. It is unclear whether or not the term “bound analyze” is referring to HGF recited in claims 1 and 14. Since HGF is the analyte being detected in the method/device, the term "bound analyte" has been interpreted as being same as HGF for the purpose of examination.

d. Claims 14-20 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: element allowing the diagnosing an inflammatory disorder based on relative levels of different forms of HGF. Claim 14 recites an immunoassay device for diagnosing an inflammatory disorder in the preamble. Therefore, claims must recite element allowing the diagnosing an inflammatory disorder based on relative levels of different forms of HGF in order for the claims to be commensurate in scope with the intended purpose of the claimed device.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1, 3, 4, 14, 19, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rudel et al. (U.S. PG Pub. No. US 2002/0115224 A1, Aug. 22, 2002) (hereinafter “Rudel") in view of Daikuhara et al. (JP 08035968 A, Feb. 6, 1996) (hereinafter “Daikuhara”).

For Daikuhara prior art reference, a machine translation of Japanese patent document has been provided.

With respect to the limitation in the preamble reciting “method for diagnosing an inflammatory disorder in an individual” and “method for evaluating inflammatory disorder in an individual" as recited in claims 1 and 21, the statements in the preamble do not provide antecedent basis for terms in the body of the claim and are not essential to understand the limitations or terms in the claim body. In addition, the preamble recites the purpose or intended use of the claimed invention. Such statements merely define the context in which the invention operates and usually will not limit the scope of the claim (MPEP 2111.02 and *DeGeorge v. Bernier*, Fed. Cir. 1985, 226 USPQ 758, 761 n.3). Therefore, diagnosing/evaluating an inflammatory disorder is an intended use and not distinguishable over the art unless the patient population is in some way distinguished or unless the method steps are distinguished. Therefore, the currently recited claim has been interpreted as a method comprising steps of contacting a body fluid sample from the individual with an immunoassay device to determine relative levels of different forms of HGF in the sample and correlating the determined levels to an inflammatory disorder.

With respect to the limitation in the preamble reciting "an immunoassay device for diagnosing an inflammatory disorder in an individual", a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. Such statements merely define the context in which the invention operates and usually will not limit the scope of the claim (MPEP 2111.02 and DeGeorge v. Bernier, Fed. Cir. 1985, 226 USPQ 758, 761 n.3). If the prior art structure is capable of performing the intended use, then it meets the claim. Therefore, the currently recited claim has been interpreted as an immunoassay device comprising at least two test areas having immobilized respectively therein reagent for binding different forms of HGF.

With respect to the limitation of "relative levels of different forms of HGF", the instant specification does not provide specific definition of "relative levels." Therefore, the term "relative levels of different forms of HGF" has been given broadest reasonable interpretation for the purpose of the examination.

With respect to claims 1, 3, 14, and 21, Rudel teaches a sensor device comprising a substrate material having a surface with multi-analyte array of biochemical sensor dots located at spatially separated predetermined positions of the planar surface (see entire document, particularly Abstract). The biochemical recognition system are directly immobilized on the surface of a sensor dot and the biochemical recognition moieties can include enzymes, antibodies, catalytic antibodies, proteins, nucleic acids and derivatives thereof such as PNA (protein nucleic acid), or LNA (locked nucleic acid),

aptamers, receptors, or cell- and tissue segments (p7, paragraph [0094]). Therefore, the teachings of Rudel reads on an immunoassay device comprising at least two test areas having immobilized therein reagents and a method comprising contacting a body fluid sample from an individual with an immunoassay device.

With respect to claim 19, Rudel teaches an immunoassay device with more than two test areas with each test areas immobilized with recognition moieties (Fig.'s 1-3).

However, Rudel is silent on specifically disclosing that the immobilized biochemical recognition moieties include reagents for binding different forms of HGF. Rudel further fails to teach steps of determining relative levels of different forms of HGF in the sample and correlating the determined levels to an inflammatory disorder.

Daikuhara teaches that the single-stranded human HGF of the inactive type contained in human body fluid, e.g. blood, plasma, lymph, sweat, urine or the like, is detected by using antibody (see entire document, particularly Abstract). The single-stranded HGF is the precursor of double-stranded HGF (active type, Abstract). In this detection, any of the following methods is used: only the single-stranded HGF is specifically detected; or the total sum of the single-stranded HGF and the double-stranded HGF is detected and the double-stranded HGF is subtracted (Abstract). The antibodies for the single-stranded HGF and the double-stranded HGF are used for both methods (Abstract). As the antibody, any of polyclonal antibody and monoclonal antibody can be used (Abstract). The single-stranded HGF is not present in a healthy person and presents only in patients of acute, chronic, fluminant hepatitis, cirrhosis or the like (Abstract).

With respect to claim 4, Daikuhara teaches an anti-HGF monoclonal antibody (Abstract).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to employ the antibodies of Daikuhara in the method and device of Rudel in order to detect both single-stranded and double-stranded HGF. The advantage of correlating the measured relative HGF levels to an inflammatory disorder (acute, chronic, fluminant hepatitis, cirrhosis or the like) provides the motivation to combine teachings of Rudel and Daikuhara. One of ordinary skill in the art would have had a reasonable expectation of success in combining teachings of Rudel and Daikuhara since the methods/device of Rudel allows detection of variety of different biochemical entities using antibodies and receptors.

17. Claims 2, 5, 6, 15, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rudel (U.S. PG Pub. No. US 2002/0115224 A1, Aug. 22, 2002) in view of Daikuhara (JP 08035968 A, Feb. 6, 1996) as applied to claims 1 and 14 above, and further in view of Nayeri (WO 02/17964 A1, Mar. 7, 2002).

Nayeri has been cited in the IDS dated July 31, 2006.

Rudel in view of Daikuhara teaches methods and immunoassay device for determining relative levels of different forms of HGF in a body fluid sample from the individual and correlating the determined levels to an inflammatory disorder as set forth above. Although Rudel teaches that a variety of different types of biochemical recognition element can be employed for the detection device and methods as set forth

above, Rudel in view of Daikuhara is silent on teaching that the immobilized reagent is a HGF receptor and that the sample includes stool.

With respect to claims 2, 5, 6, 15, and 16, Nayeri teaches activated form of HGF binds to c-MET (HGF receptor, see entire document, particularly p1, lines 17-28). Nayeri further teaches that a variety of different samples including feces/stool be analyzed for the presence of HGF during an ongoing infectious conditions (p10, lines 13-24).

The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. at ___, 82 USPQ2d at 1395; *Sakraida* v. AG Pro, Inc., 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); *Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152, 87 USPQ 303, 306 (1950). "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to employ c-MET of Nayeri in the device/methods of Rudel in view of Daikuhara in order to detect double-stranded/active form of HGF. One

skilled in the art would have employed c-MET of Nayeri for the detection of double-stranded/active form of HGF since c-Met would allow specific binding to HGF for the same function of specifically detecting HGF.

In addition, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to detect HGF levels in feces/stool samples as taught by Nayeri in the device/methods of Rudel in view of Daikuhara in order to monitor ongoing infections. One skilled in the art would have been motivated to include feces/stool sample for HGF analysis with a reasonable expectation of success as Nayeri teaches a correlation of an inflammatory disorder and HGF levels in feces/stool.

18. Claims 7, 8, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rudel (U.S. PG Pub. No. US 2002/0115224 A1, Aug. 22, 2002) in view of Daikuhara (JP 08035968 A, Feb. 6, 1996) as applied to claims 1, 14, and 19 above, and further in view of Duke-Cohan et al. (U.S. Patent No. 6,265,551 B1, July 24, 2001) (hereinafter "Duke-Cohan").

Rudel in view of Daikuhara teaches methods and immunoassay device for determining relative levels of different forms of HGF in a body fluid sample from the individual and correlating the determined levels to an inflammatory disorder as set forth above. However, Rudel in view of Daikuhara is silent on teaching an additional immobilized reagent comprising carboxymethyl dextran.

Duke-Cohan teaches a surface coated with carboxymethyl dextran as a control surface for specific binding assays (see entire document, particularly column 5, lines 26-45).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to immobilize carboxymethyl dextran on the surface of the sensor device of Rudel in view of Daikuhara as taught by Duke-Cohan in order to provide control surface for the detection assays. The advantage of having a control surface provides the motivation for combining the teachings of Rudel in view of Daikuhara and Duke-Cohan with a reasonable expectation of success.

19. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rudel (U.S. PG Pub. No. US 2002/0115224 A1, Aug. 22, 2002) in view of Daikuhara (JP 08035968 A, Feb. 6, 1996) as applied to claim 1 above, and further in view of Latov et al. (U.S. PG Pub. No. US 2002/0177161 A1, published Nov. 28, 2002 and filed Apr. 3, 2001) (hereinafter "Latov").

Rudel in view of Daikuhara teaches methods and immunoassay device for determining relative levels of different forms of HGF in a body fluid sample from the individual and correlating the determined levels to an inflammatory disorder as set forth above. However, Rudel in view of Daikuhara is silent on teaching a step of contacting the body fluid sample with dextran prior to contact with immunoassay device.

Latov teaches an SPR analysis of sample. Prior to analysis, all specimens were diluted using a buffer containing dextran, which is used to reduce nonspecific binding (see entire document, particularly p4, paragraph [0071]).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to treat the sample with dextran in the method of Rudel in view of Daikuhara as taught by Latov in order to reduce nonspecific binding during the detection assay. The advantage of reducing nonspecific binding provides the motivation for combining the teachings of Rudel in view of Daikuhara and Latov with a reasonable expectation of success.

20. Claims 10, 17, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rudel (U.S. PG Pub. No. US 2002/0115224 A1, Aug. 22, 2002) in view of Daikuhara (JP 08035968 A, Feb. 6, 1996) as applied to claims 1 and 14 above, and further in view of Finian et al. (U.S. Patent No. 4,997,278, Mar. 5, 1991) (hereinafter "Finian").

Rudel in view of Daikuhara teaches methods and immunoassay device for determining relative levels of different forms of HGF in a body fluid sample from the individual and correlating the determined levels to an inflammatory disorder as set forth above. Although Rudel teaches a surface plasmon resonance device for translating a level of bound analyte in a test area into a measurable signal (p1, paragraph [0003]), Rudel in view of Daikuhara is silent on teaching that the biosensor produces electrical signal proportional to each bound analyte

Finian teaches SPR sensor for conducting immunoassays (see entire document). An array of detectors can be arranged to generate electrical signals indicative of variations of intensity of light with position across a beam (see entire document, particularly column 5, lines 12-20). The SPR effect dictates that strong absorption will occur at a particular angle as determined by material in the fluid to which the reflective layer is exposed (column 5, lines 12-20). These electrical signals are sampled and digitized and fed to a suitable analyzing arrangement which may include a microprocessor or larger computer (column 5, lines 12-20).

The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. at ___, 82 USPQ2d at 1395; *Sakraida* v. AG Pro, Inc., 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); *Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152, 87 USPQ 303, 306 (1950). "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to employ well known detection method of Finian, which includes an array of

detectors for generating electrical signals indicative of analyte binding, in the method of Rudel in view of Daikuhara in order to simultaneously detect binding reactions on the SPR sensor surface. The advantage of providing electrical signals, which can be processed by a computer, provides the motivation to combine teachings of Rudel in view of Daikuhara and Finian with a reasonable expectation of success.

21. Claims 11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rudel (U.S. PG Pub. No. US 2002/0115224 A1, Aug. 22, 2002) in view of Daikuhara (JP 08035968 A, Feb. 6, 1996) as applied to claim 1 above, and further in view of Matsuno et al. (*Res. Comm. Mol. Path. Pharm.*, 1997, Vol. 97, pp25-27) (hereinafter "Matsuno").

Although Matsumo has been provided by the applicant on July 31, 2009, the IDS dated July 31, 2006 does not cite Matsuno. Therefore, Matsuno reference has been included in the PTO-892 form with this Office Action.

Rudel in view of Daikuhara teaches methods and immunoassay device for determining relative levels of different forms of HGF in a body fluid sample from the individual and correlating the determined levels to an inflammatory disorder as set forth above. However, Rudel in view of Daikuhara is silent on teaching a step of contacting the body fluid sample with dextran prior to contact with immunoassay device.

Matsuno teaches that HGF levels change in inflammatory bowel diseases (see entire document, particularly Abstract).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to correlate HGF levels of Rudel in view of Daikuhara to inflammatory bowel diseases since Matsuno teaches that HGF levels change in inflammatory bowel diseases. The advantage of correlating HGF levels to inflammatory bowel diseases provides the motivation for combining the teachings of Rudel in view of Daikuhara and Matsuno with a reasonable expectation of success.

Prior Art of Record

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

- Kern et al. (*Cytokine*, 2001, Vol. 14, pp170-176) teaches increases in HGF concentration in cerebrospinal fluid in acute bacterial meningitis (see entire document).
- Srivastava et al. (*J. Ped. Gastro. Nutr.*, 2001, Vol. 33, pp548-553) teaches that serum HGF levels are elevated in individuals with Crohn disease and ulcerative colitis (see entire document).

Conclusion

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to UNSU JUNG whose telephone number is (571)272-8506. The examiner can normally be reached on M-F: 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Unsu Jung/
Unsu Jung
Primary Examiner
Art Unit 1641